Transient Cold Agglutinin Disease with Mycoplasma Infection

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Abstract
Cold agglutinins are autoantibodies and are often present in the sera of healthy individuals. They assume importance when the thermal reactivity of these antibodies approaches body temperature. This communication describes a case of cold hemagglutinin disease with Mycoplasma pneumoniae infection detected during routine laboratory investigations. The patient was managed conservatively.

Introduction
Cold agglutinin syndrome is a hemolytic anemia associated with cold reactive autoantibodies and accounts for 16-32% of all cases of immune hemolysis. Potent cold agglutinins, that react with all cells including the patient’s own, can create special problems, specially when reactivity persists at temperatures above room temperature. The acute form of cold agglutinin syndrome is often secondary to lymphoproliferative disorders or Mycoplasma pneumoniae infection.

Case Report
A twenty five year male presented with chief complaints of fever, cough, chest pain and headache of 10 days duration. There was no pallor, jaundice or cyanosis on general physical examination. Chest examination revealed bilateral crepitations. A blood sample was sent for routine hemogram but results could not be obtained from the automated cell counter. Manual processing showed mild anemia (9.4 g/dl) with mildly elevated total leucocyte count and marked difficulty was encountered in making peripheral smears. Careful examination of the tube containing the anticoagulated (EDTA) sample showed auto-agglutination. This macroscopically visible auto-agglutination was exaggerated at 4°C and disappeared at 37°C. To determine the nature of the agglutinins, the reactivity of the patient’s serum with autologous cells and group ‘O’ adult cells was studied at different temperatures. The results are shown in Table 1. The direct Coomb’s test using polyspecific Coomb’s reagent (anti-C3d and IgG) was strongly positive while the indirect Coomb’s test was negative. The peripheral blood examination confirmed agglutination and showed moderate anisopoikilocytosis, polychromasia and few spherocytes. Reticulocyte count was raised (6.2%) and there was indirect hyperbilirubinemia (total bilirubin = 2.8 mg/dl, unconjugated = 2.55 mg/dl). Sputum for AFB was negative. X ray chest revealed a pneumonic patch in the left lung. IgM antibody for Mycoplasma pneumoniae was positive. A diagnosis of cold agglutinin disease in association with M. pneumoniae infection was made. The patient was shifted to a warm room, started on systemic antibiotics and given supportive care. He soon showed improvement.

Discussion
Cold reactive autoantibodies may be benign or pathologic depending primarily on the thermal reactivity of these antibodies. Benign cold autoantibodies are often seen in healthy adults, are reactive below 22°C and have a titre of less than sixty-four. Pathologic cold reactive antibodies have a higher thermal amplitude and manifest either as a chronic cold agglutinin disease or as an acute transient hemolytic anemia as seen in association with respiratory tract infections.

Cold agglutinins are IgM autoantibodies which effectively activate the classical complement cascade. In cold haemagglutinin disease (CHAD) complement is the only protein detected on the red cells in almost all the cases, since IgM dissociates from red cells at warmer temperatures. Regulatory proteins convert the red cell bound C3 and C4, to C3d, C3dg and C4d. It is the anti-C3d component of polyspecific AHG that accounts for the positive DAT as was seen in our case. The index case had a strong positive DAT using polyspecific AHG (anti-C3d and anti-IgG) and the indirect Coomb’s test was negative. The reactivity of the patient’s serum with autologous cells and group O adult cells showed that the antibodies were most reactive at 4°C. Reactivity was also present at 22°C but decreased at warmer temperatures and disappeared at 37°C (Table 1). Hematologic and biochemical evidence for hemolysis was also forthcoming and a diagnosis of transient CHAD was made. In addition there was evidence of recently acquired Mycoplasma pneumoniae infection (positive IgM for M. pneumoniae). In Mycoplasma infections the auto-agglutinin is usually polyclonal IgM with anti-I specificity. The autoantibodies in this patient were IgM since they were saline reacting and indirect Coomb’s test using IgG monospecific Coomb’s sera was negative. Though the autoantibodies reacted strongly with group ‘O’ adult cells, the reactivity with cord red blood cells was not studied and so anti-I specificity could not be confirmed. Stronger reactions with adult red cells than with cord red cells indicate anti-I specificity. It is believed that the M. pneumoniae organism possesses an I-like antigen which stimulates the formation of cross-reacting anti-I antibodies. Alternatively it has also been postulated that the organism modifies the I antigen on the red cell membrane thereby rendering it antigenic.

In CHAD it is the reactivity of the cold agglutinin at warm...
temperatures and not the antibody titre that correlates with the severity of the disease. Our patient had cold agglutinin titre of 1:256 and the autoantibodies were most reactive at 4°C. The reactivity decreased at warmer temperatures (22°C to 30°C) and completely disappeared at 37°C. In another similar case reported by Wilson et al, the titre of autoantibodies was only 1:512 but the patient also had recurrent arterial thrombosis.³

Our patient was managed conservatively. Besides receiving antibiotics and antipyretics, he was kept in a warm environment and given supportive care. There was no need of any transfusion therapy. He was counseled regarding his problem and advised to avoid cold temperatures.

This case was detected incidentally in the laboratory and then further correlated with the patient’s clinical profile. The present communication highlights the fact that often it is the laboratory or the blood bank that gives the first indication that a patient could be having cold agglutinin disease. Hence the need for laboratory personnel to be aware of this entity so that timely diagnosis can be made and further complications avoided.

References